Smallpox Vaccination: Normal and Adverse Reactions

The material in this document was taken from: 1) CDC. Smallpox vaccination and adverse reactions: guidance for clinicians. *MMWR* 2003;52(No. RR-4); 2) Fulginiti VA, et al. Smallpox vaccination: a review, parts I and II. *Clin Infect Dis* 2003;37:241-71; 3) DoD. Smallpox Vaccine – Cardiac Related Reactions; November 4, 2003; 4) CDC. *Medical Management of Smallpox (Vaccinia) Vaccine Adverse Reactions: Vaccinia Immune Globulin and Cidofovir*; February 11, 2003; and 5) CDC. Update: adverse events following civilian smallpox vaccination - United States, 2003. *MMWR* 2004; 53(5):106-7. Pictures are from the Centers for Disease Control & Prevention (CDC).

Description of the Vaccine

Smallpox vaccine is made from live vaccinia virus; it does not contain variola virus, the causative agent of smallpox. Dryvax® (Wyeth Laboratories Inc.), a calf-lymph-derived vaccine, is the smallpox vaccine currently in use. Smallpox vaccine is administered into the superficial layers of the skin through multiple punctures using a small bifurcated needle.

Contraindications to Smallpox Vaccine

Contraindications to smallpox vaccination in the pre-outbreak setting (i.e., in the absence of smallpox cases) are the following:

Smallpox vaccination is contraindicated for persons who have the following conditions or who have a household or close contact* with the following conditions:

1) a history of atopic dermatitis (commonly referred to as eczema), irrespective of disease severity or activity;
2) active acute, chronic, or exfoliative skin conditions that disrupt the epidermis;
3) pregnant women or women who desire to become pregnant in the 28 days after vaccination; and
4) persons who are immunocompromised as a result of HIV or AIDS, autoimmune conditions, cancer, radiation treatment, immunosuppressive medications, or other immunodeficiencies.

Additional contraindications that apply only to vaccination candidates but do not include their close contacts are:

1) diagnosed by a physician as having a heart condition, or the presence of 3 or more of the following risk factors:
   a) high blood pressure
   b) high blood cholesterol
   c) diabetes or elevated blood glucose levels
   d) a first-degree relative (e.g., mother, father, sister or brother) who had a heart condition before age 50
   e) smoke cigarettes now;
2) persons with smallpox vaccine-component allergies;
3) women who are breastfeeding;
4) persons taking topical ocular steroid medications;
5) persons with moderate-to-severe intercurrent illness; and
6) persons aged <18 years.

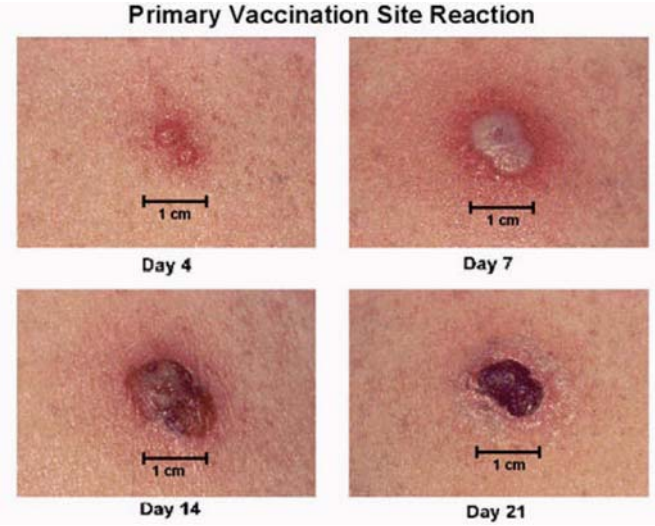
In addition, history of Darier disease is a contraindication in a potential vaccinee and a contraindication if a household contact has active disease.

*Includes all persons with prolonged intimate contact with the potential vaccinee, including those having the potential for direct contact with the vaccination site (e.g., sexual contacts).

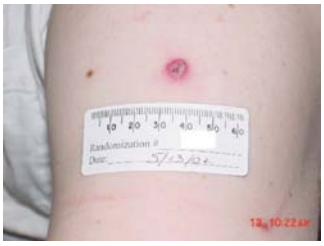
In the event of a smallpox outbreak, specific guidance will be disseminated by the Centers for Disease Control and Prevention (CDC) regarding populations to be vaccinated and specific contraindications to vaccination.

Normal Response to Vaccination

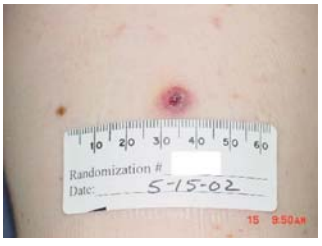
Following vaccination, the vaccinia virus replicates in the dermis of the skin. In first-time (primary) vaccinees, the following sequence of events would normally be expected to occur at the vaccination site: 3-5 days after vaccination, a papule forms at the vaccination site. The papule becomes vesicular with surrounding erythema (approximately day 5-8), then pustular, and usually enlarges to reach maximum size in 8-10 days. The pustule dries from the center outward and forms a dark brown or black scab that separates 14-21 days after vaccination, usually leaving a pitted scar.



In persons who have received smallpox vaccine in the past, the nature of the response to revaccination depends on the degree of residual immunity that is present. Revaccinees may show a typical primary reaction with progression of the vaccination site as described in the preceding paragraph. However, revaccinees having some remaining immunity to vaccinia as the result of their previous vaccination(s) may experience a more rapid progression of the vaccination site.



Revaccinee, Day 8



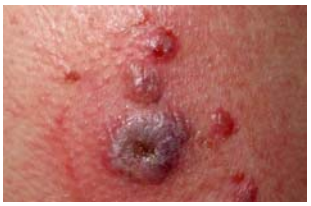
Revaccinee, Day 10

A range of expected systemic and local reactions can occur after vaccination. About 1 week after vaccination, certain systemic symptoms are expected in some vaccinees: **a)** temperature >37.7°C in the first 3 weeks after vaccination (2%-16%); **b)** malaise, myalgia, headache, chills, nausea, and

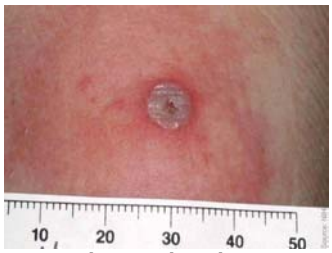
fatigue (0.3%-37%); **c)** pruritis at the vaccination site (common); **d)** soreness at the vaccination site (almost universal); **e)** regional lymphadenopathy (25%-50%); and **f)** intense erythema ringing the vaccination site (common). Symptomatic treatment should be utilized.

Expected, normal local events following vaccination occur infrequently (2%-6% of vaccinees enrolled in clinical trials), and require only symptomatic treatment. These events include **a)** the appearance of satellite lesions, which are benign, secondary vaccinial lesions within ~2.5 cm (1 in) of the primary vaccination site, and which should be cared for in the same way as the vaccination site; **b)** viral lymphangitis with a visible track toward regional lymph nodes in the axilla (must be differentiated from bacterial infection); **c)** local edema, often enlarging the upper arm's circumference and causing discomfort and pain; and **d)** intense inflammation surrounding the papule (viral cellulitis).

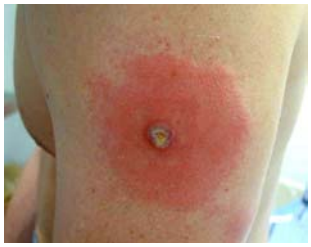
Large vaccination reactions or "robust takes" (>7.5 cm area of erythema with swelling, warmth, and pain) at the site of inoculation occur in approximately 10% of first-time vaccinees and are expected variants of the typical evolution of the vaccination site. More information on robust takes is provided in Table 1.



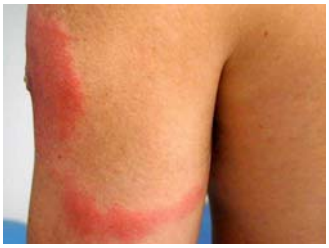
Satellite Lesions



Edema and erythema



Robust take with lymphangitis



Robust take with lymphangitis

Additional pictures of normal reactions to smallpox vaccination, including normal variants, are available from CDC at http://www.bt.cdc.gov/training/smallpoxvaccine/reactions/normal.html.

Potential Transmission of Vaccinia

Viral replication and shedding at the vaccination site begin 2-5 days postvaccination. As a consequence, unintended transmission of vaccinia to a second location on the vaccinee or to a close contact is possible until the scab that develops at the site separates from the skin (approximately 2-3 weeks). Viral shedding might be of shorter duration among revaccinees. Transmission to others has usually required close interaction and has occurred most often in the home. (Note that no data exist to indicate that vaccinia transmission occurs by aerosolization.) It is very important that each vaccinee take appropriate precautions to prevent transmission of vaccinia from their vaccination site to other areas of their own body (autoinoculation), or to their close contacts (contact transmission). Correct hand hygiene after changing bandages and after other contact with the vaccination site prevents the majority of these inadvertent inoculations. The Attachment (page 6), taken from the Vaccine Information Statement (VIS) for smallpox vaccine, contains specific recommendations for care of the vaccination site.

Evidence of Successful Vaccination

Formation by days 6-8 postvaccination of a papule, vesicle, ulcer, or crusted lesion, surrounded by an area of induration, signifies a response to vaccination; this event is referred to as a "major reaction" or a "take," and usually results in a scar. During the smallpox eradication era, persons with vaccination scars had much lower attack rates when exposed to smallpox cases than did nonvaccinated persons. Therefore, a take has been a surrogate correlate of immunity to smallpox. Although the level of antibody that protects against smallpox infection is unknown, >95% of first-time vaccinees (i.e., persons receiving their first dose of smallpox vaccine) have increased neutralizing or hemagglutination inhibition antibody titers.

Adverse Reactions

Smallpox vaccine is a generally safe and effective means to prevent smallpox, but adverse reactions following vaccination can occur. These adverse reactions range from mild and self-limited to severe and life-threatening. In the past, approximately 1-2 primary vaccinees died per million vaccinated. Certain smallpox vaccine reactions are similar to those caused by other vaccines (e.g., high fever, anaphylaxis, and erythema multiforme). Other adverse reactions specific to smallpox vaccination include inadvertent inoculation, ocular vaccinia, generalized vaccinia, eczema vaccinatum, progressive vaccinia, postvaccinial encephalopathy and encephalomyelitis, and fetal vaccinia (see Table 1, which besides adverse reactions also includes robust take, generally considered a normal variant). Vaccinia-specific complications can occur among vaccinees, or among their contacts who have been inadvertently infected with vaccinia.

Data from recent smallpox vaccinations have been found to be consistent with a causal association between vaccination and myopericarditis. The Department of Defense reported in early November 2003 that, among 515,000 military personnel receiving smallpox vaccine since the preceding December, 63 cases of myocarditis and/or pericarditis had been identified. Symptoms most often appeared 7-14 days after vaccination. Most of these cases had clinical conditions that were mild to moderate; the condition was severe in two cases. No susceptibility criteria are known. In contrast, some deaths resulting from coronary artery-related disease occurring within 1 month after vaccination appear to be only temporally related to the vaccine, rather than being caused by the vaccine itself. However, in order to be cautious, a history of a "heart condition," or the presence of certain cardiac risk factors, is currently included as a contraindication to smallpox vaccine in the pre-event setting.

Pictures of adverse reactions are available from CDC at http://www.bt.cdc.gov/training/smallpoxvaccine/reactions/adverse.html.

Table 1. Summary of vaccinia-related adverse events

Adverse event	Description	Risk factor	Treatment
Eczema vaccinatum (EV)	• High fever • Generalized lymphadenopathy with extensive vesicular and pustular eruption • Onset: concurrently or shortly after local vaccinial lesion in vaccinee, or in contacts, 5–19 days after suspected exposure • Risk for secondary bacterial or fungal infections • Virus recovered from lesions • High morality rate with poor prognosis	• History of eczema or atopic dermatitis irrespective of disease activity or severity • Less frequently, persons without a history of dermatological conditions	• Prompt evaluation and diagnosis • Infection-control precautions • Might require multiple doses of vaccinia immune globulin (VIG) (cidofovir, second-line therapy) • Hemodynamic support • Volume and electrolyte repletion • Observe for secondary skin infections
Progressive vaccinia (PV)	• Nonhealing vaccination site • Painless progressive (central) necrosis at the vaccination site • Occasional metastatic lesions in skin, bones, and viscera • No inflammation initially • Absence of inflammatory cells on histopathological examination • Inflammation weeks later • Bacterial infection might develop • Differential diagnosis: severe bacterial infection, severe chickenpox, disseminated herpes simplex, and other necrotic conditions • Prognosis: poor, despite therapy	• Humoral and cellular immunocompromise (e.g., malignancy, HIV/ AIDS, severe combined immunodeficiency syndrome (SCIDS), or hypogammaglobulinemia) • Protective level of T-cell count or humoral immunity unknown	• Prompt evaluation and diagnosis • Infection-control precautions • Might require multiple doses of VIG (cidofovir second-line therapy) • Surgical debridement of progressive necrotic lesions not proven useful
Postvaccinial encephalitis (PVE) or encephalomyelitis (PVEM)	• Diagnosis of exclusion • Appears similar to postinfectious encephalomyelitis or toxic encephalopathy caused by other agents • Abrupt onset of symptoms: fever, headache, malaise, lethargy, vomiting, meningeal signs, seizures, paralysis, drowsiness, altered mental status, or coma • Age <2 years (encephalopathy): cerebral vascular changes occurring 6–10 days postvaccination • Age ≥2 years (encephalomyelitis): demyelinating changes occurring 11–15 days postvaccination • Cerebral spinal fluid (CSF): normal or nonspecific; monocytosis, lymphocytosis, or elevated protein • Prognosis: mortality, 25%; neurological sequelae, 25%; complete recovery, 50%	• Age <1 year	• Intensive supportive care • Anticonvulsants as needed • VIG not recommended • Antiviral role unclear • Use of modern imaging studies has not been evaluated
Fetal vaccinia (FV)	• Incidence: rare (<50 reported cases) • Route of transmission: unknown • Outcomes: premature birth, fetal loss, high mortality • Not associated with congenital anomalies	• Cases in all trimesters of pregnancy • Greatest risk, third trimester	• Efficacy of VIG unknown • Antivirals not recommended
Generalized vaccinia (GV)	• Maculopapular or vesicular rash • Onset: 6–9 days postvaccination • Nontoxic, with or without fever • Differential diagnosis: erythema multiforme (EM), varicella, inadvertent inoculation, progressive vaccinia (PV), and smallpox	• Hematogenous spread • Lesions contain vaccinia • More serious among immunocompromised persons	• Usually self-limited in immunocompetent person • Infection-control precautions • VIG usually not indicated • Anti-inflammatory medications • Antipruritic medications • Antivirals usually not indicated
Inadvertent inoculation	• Most common complication • Physical transfer of vaccinia virus from a vaccination site to second site on the vaccinee or to a close contact of vaccinee	• Manipulation of vaccination site • Children aged <4 years • Conditions that disrupt the epidermis (e.g., burns, severe acne, or psoriasis)	• Usually self-limited • Resolution in 3 weeks • Infection-control precautions • VIG if extensive body surface involved or severe ocular disease (cidofovir, second-line therapy)

Table 1. Summary of vaccinia-related adverse events (Continued)

Adverse event	Description	Risk factor	Treatment
Ocular vaccinia **Inadvertent periocular or ocular implantation with vaccinia virus** **Can range from mild to severe**	Keratitis • Marginal infiltration or ulceration with or without stromal haze/infiltration Conjunctivitis • Hyperemia, edema, membranes, focal lesions, fever, lymphadenopathy Blepharitis • Lid pustules on or near the lid margin, edema, hyperemia, lymphadenopathy, cellulitis, fever	• Manipulation of vaccination site, followed by eye rubbing • More likely with conditions that cause eye itching and scratching (conjunctivitis, corneal abrasion/ulceration)	• Ophthalmologic consultation • Certain ophthalmologists consider off-label topical antiviral medications • Topical prophylactic antibacterial medications for keratitis • VIG for severe blepharitis and blepharoconjunctivitis (without keratitis) • VIG not indicated for isolated keratitis • VIG considered for keratitis with vision-threatening conditions • VIG indicated for keratitis with life-threatening conditions that require VIG
Erythema multiforme (EM) and Stevens-Johnson Syndrome (SJS)	• Typical bull's eye (target) lesions • Hypersensitivity reaction • Pruritis • Onset: 10 days postvaccination • Can progress to SJS	• No known risk factors	• Antipruritic medications • VIG not indicated • Hospitalization and supportive care for SJS • Steroid use for SJS is controversial
Pyogenic infections of vaccination site	• Uncommon • Onset: 5 days postvaccination • Fever not specific for bacterial infection • Fluctuance at vaccination site	• More frequent in children (touching vaccination site)	• Gram stain • Bacterial culture • Antibacterial medications, if clinically indicated • No topical medications
Robust take (RT)	• >7.5 cm with swelling, warmth, and pain at vaccination site • Fluctuant lymph nodes not expected • Peak symptoms: 8–10 days postvaccination • Nonprogressive • Improvement in 24–72 hours	• Might be more likely among first-time vaccinees	• Observation most important • Antibacterial medications not indicated • Rest affected limb • Antipruritic medications • Anti-inflammatory medications • No salves or ointments
Tape adhesive reactions	• Sharply demarcated raised lines of erythema that correspond to adhesive placement • Local pruritis • No systemic illness	• Sensitivity to adhesives	• No salves, ointments, or topical/oral steroids • Frequent bandage changes • Periodic bandage removal

During January 24-December 31, 2003, smallpox vaccine was administered to 39,213 civilian health-care and public health workers to help prepare the United States for a possible terrorist attack using smallpox virus. Table 2 describes, for these individuals during this period, the number of cases of selected adverse events associated with the vaccine and reported through the Vaccine Adverse Event Reporting System (VAERS).

If certain types of adverse reactions (e.g., generalized vaccinia, inadvertent inoculation) are suspected, testing for the presence of vaccinia virus in lesions may be helpful. Such testing is available through the Missouri State Public Health Laboratory (MSPHL), but prior consultation is required before specimens can be sent – call 800/392-0272 (24 hours a day - 7 days a week). Information on vaccinia testing from MSPHL is available at http://www.dhss.state.mo.us/Lab/RashInvestigation.htm.

Vaccinia immune globulin (VIG) and cidofovir are available for the treatment of certain serious smallpox vaccine adverse events, including progressive vaccinia, eczema vaccinatum, generalized vaccinia (severe form or if underlying illness), and inadvertent inoculation (if judged to be severe due to the number of lesions, toxicity of the affected individual, or significant pain). VIG is recommended as the first line of therapy; cidofovir may be considered as a secondary treatment. VIG and cidofovir are available through CDC under Investigational New Drug (IND) protocols. Requests for these drugs must come through the state health department. The Missouri Department of Health and Senior Services (DHSS) can be contacted 24 hours a day - 7 days a week at 800/392-0272.

When managing patients with suspected or confirmed adverse reactions to smallpox vaccine, consultation with appropriate clinical specialists (e.g., infectious disease, dermatology, ophthalmology) is recommended. Consultation with DHSS staff and, as indicated, with experts at CDC, is available – call 800/392-0272.

When evaluating and caring for persons with suspected or confirmed adverse reactions to smallpox vaccine, health care providers should use Standard Precautions and, if indicated, Contact Precautions.

Table 2. Number of cases* of selected adverse events associated with smallpox vaccination among civilians, by type — United States, January 24–December 31, 2003

Adverse events	No. new cases (August 9–December 31)			Total no. cases (January 24–December 31)		
	Suspected†	Probable§	Confirmed¶	Suspected	Probable	Confirmed
Eczema vaccinatum	—**	—	—	—	—	—
Fetal vaccinia	—	—	—	—	—	—
Generalized vaccinia	—	—	—	2	—	1
Inadvertent inoculation, nonocular	—	—	—	11	—	9
Ocular vaccinia	—	—	—	1	—	2
Progressive vaccinia	—	—	—	—	—	—
Erythema multiforme major (Stevens-Johnson syndrome)	—	—	—	—	—	—
Myo/pericarditis	—	—	—	16	5	—
Postvaccinial encephalitis or encephalomyelitis	—	—	—	1	—	—
Pyogenic infection of vaccination site	—	—	—	—	—	—

* Under investigation or completed as of December 31, 2003; numbers and classifications of adverse events will be updated regularly on CDC's website at http://www.cdc.gov/od/oc/media/spadverse.htm.
† Events are classified as suspected if they have clinical features compatible with the diagnosis, but either further investigation is required or additional investigation of the case did not provide supporting evidence for the diagnosis and did not identify an alternative diagnosis.
§ Events are classified as probable if possible alternative etiologies are investigated and excluded and supportive information for the diagnosis is found.
¶ The first six events listed are classified as confirmed if virologic tests are positive. The last four events are classified as confirmed on the basis of diagnostic testing (e.g., histopathology); confirmation of events thought to be immunologically mediated (i.e., erythema multiforme, myo/pericarditis, postvaccinial encephalitis, or encephalomyelitis) does not establish causality.
** No cases reported.

Links to more detailed information for clinicians on smallpox vaccine reactions (both expected and adverse) and their diagnosis and management are available at http://www.dhss.state.mo.us/BT_Response/Med/m_smallpox_vacc.htm (scroll down to the sections entitled "Normal Reactions Following Smallpox Vaccination" and "Adverse Reactions & Management").

DHSS's Communicable Disease Reporting Rule (19 CSR 20-20.020) requires that "[d]iseases, findings or adverse reactions that occur as a result of inoculation to prevent smallpox" be reported to the local public health agency or to DHSS "within twenty-four (24) hours of first knowledge or suspicion." Specific conditions here include accidental administration, inadvertent autoinoculation, bacterial infection of the site of inoculation, congenital vaccinia, contact vaccinia (i.e., vaccinia virus infection in a contact of a smallpox vaccinee), eczema vaccinatum, erythema multiforme, generalized vaccinia, post-vaccinial encephalitis, progressive vaccinia, and vaccinia keratitis. Reports to DHSS can be made by calling 800/392-0272.

A large number of links to clinical information on smallpox vaccine and smallpox disease are available on DHSS's Emergency Response & Terrorism web site at: http://www.dhss.state.mo.us/BT_Response/Bio_Med.htm (click on "Smallpox Vaccine" or "Smallpox"). Consultation with DHSS staff on these or any other bioterrorism-associated conditions is always available at 800/392-0272.

The Vaccine Information Statement for smallpox vaccine is available at http://www.bt.cdc.gov/agent/smallpox/vaccination/needtoknow.asp.

Center for Emergency Response & Terrorism, and
Division of Environmental Health & Communicable Disease Prevention
Missouri Department of Health & Senior Services
March 2004

Attachment
Vaccination Site Care Instructions for Persons Who Have Received Smallpox Vaccine

6 What should you expect after vaccination?

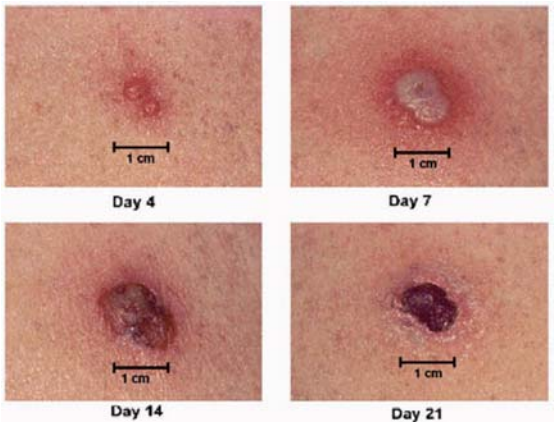
Normal Reactions

Week 1: Three or 4 days after vaccination, a red, itchy bump will form at the "vaccination site". Most times, this spot is about the size of a dime. It can be larger than 3 inches. The bump becomes a blister. It will fill with pus and then start to drain.

A health care provider should check your vaccination site 6–8 days after you get the vaccine to make sure the vaccination worked and everything is o.k.

Week 2: The blister will dry up and a scab will form.

Week 3: The scab will fall off. It will leave a small scar.



The lymph nodes under your arm may swell and be sore. The vaccination site may itch. You may also feel tired, have a mild fever, headache, or muscle aches.

You may not get a blister if the vaccine did not work properly or if you are already immune to smallpox. In this case, you will need to get the vaccine again. If you still do not get a blister after getting the vaccine a second or third time, a health care provider will tell you if you are, or are not, considered immune.

What You Will Need to Do

The virus in the vaccine is alive. It can be spread from the vaccination site to other parts of your body or to other people through close physical contact. This can happen until the scab falls off.

In the past, the vaccine virus was spread from vaccinated people to others about 2 to 6 times out of every 100,000 people vaccinated for the first time (this usually happened between people who lived together).

To Help Prevent Spread of the Virus:

- **Cover the area** loosely with a gauze bandage held in place with first aid tape. While at work, health care workers should also cover the gauze with a semi-permeable bandage (this type of bandage allows air to flow through but not fluids).
- Change the bandage often (at least every 3 days).
- **Try not to touch your vaccination site.**
- Do not let others touch the site or items that have touched it such as bandages, clothes, sheets, or towels.
- Always **wash your hands** with soap and water or alcohol-based hand wash if you touch the site or if you touch bandages, clothes, sheets, or towels that have touched the site.
- Keep the vaccination site dry. If the gauze bandage gets wet, change it right away. Cover your vaccination site with a waterproof bandage while bathing.
- Don't scratch or put ointment on the vaccination site.
- Don't touch your eyes, any part of your body, or another person after changing the bandage or touching the vaccination site until you have washed your hands.
- Wear a shirt that covers the vaccination site and bandage. This helps protect those you have close contact with such as young children or the person you share a bed with.
- Don't share towels.
- Do your own laundry. Use a separate laundry hamper for clothes, towels, sheets, and other items that may come into contact with your vaccination site or pus from the site. Machine wash items that have touched the vaccination site in hot water with detergent and/or bleach.
- Put used bandages in plastic zip bags, then throw them away in the regular trash.
- After the scab falls off, put it in a plastic zip bag and throw it away.

If you do not feel like you can follow these instructions, do not get vaccinated.

Vaccine Information Statement: Smallpox Vaccine. November 15, 2003
http://www.bt.cdc.gov/agent/smallpox/vaccination/pdf/smallpox-vis.pdf